ANALYSIS OF SUBCLINICAL HYPOTHYROIDISM IN ELDERLY WOMEN

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CERTIFICATE

This is to certify that the dissertation titled "**ANALYSIS OF SUBCLINICAL HYPOTHYROIDISM IN ELDERLY WOMEN**" is the bonafide original work of DR**. S. BALASUBRAMANIAM,** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in **SEPTEMBER 2006**. The Period of study was from June 2005 to December 2005.

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DECLARATION

I, **DR. S. BALASUBRAMANIAM,** solemnly declare that dissertation titled **"ANALYSIS OF SUBCLINICAL HYPOTHYROIDISM IN ELDERLY WOMEN"** is a bonafide work done by me at Government Stanley Medical College and Hospital during 2005 under the guidance and supervision of my unit chief **PROF. R. DEENADAYALAN, M.D**., Addl. Professor of Medicine.

This dissertation is submitted to Tamilnadu DR. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine.**

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CONTENTS

INTRODUCTION

Subclinical hypothyroidism (SH) is characterized by an elevated serum concentration of thyroid stimulating hormone (TSH) and normal serum concentration of free thyroxine (FT4) in the presence or absence of symptoms[1.]

This biochemical state has been given a variety of other names, including mild thyroid failure, as well as compensated, early, late, minimally symptomatic, and pre-clinical hypothyroidism [2,3].

Although the term subclinical hypothyroidism is widely used, mild hypothyroidism may be more appropriate[4].

Subclinical hypothyroidism is a common disorder with prevalence ranging from 1–10% of the, mostly adult, population [5-9], with the highest rate approaching 26% in elderly women [6,10,11]. In a study conducted in Saudi Arabia the prevalence in elderly women more than 50 years of age reached 35%.

Clinical manifestations of subclinical hypothyroidism include abnormal lipid metabolism [12-14], cardiac dysfunction [15,16], and neurological and mental dysfunction [17], and several cross-sectional studies have suggested that it confers an elevated risk of atherosclerosis and coronary heart disease [11,18]. However, neither of these associations has been confirmed by others [19,20]. This discrepancy may reflect the small size of the studies or participation in studies limited to one sex.

Also, only few longitudinal studies have been conducted. The relationship between subclinical hypothyroidism and cardiovascular disease is therefore controversial, and possible outcomes of the condition remain unclear. Importantly, several previous studies suggesting that thyroid autoimmunity is a risk factor for coronary heart disease [18,21,22] remain surrounded by controversy [20,23].

Women with subclinical hypothyroidism did not differ from controls with regard to BMI, hypertension, and diabetes mellitus in previous studies[11,24].

The present study has been performed to estimate the prevalence of subclinical hypothyroidism and its relation to hypertension, diabetes, and ischemic heart disease among women above the age of 50 years attending Medical outpatient clinic at Government Stanley Medical College and Hospital.

AIM OF THE STUDY

- To estimate the prevalence of Subclinical Hypothyroidism among women above the age of 50 years.
- To study the relationship of Subclinical Hypothyroidism to Hypertension, Diabetes Mellitus and Ischemic Heart Disease in those patients.

REVIEW OF LITERATURE

The thyroid gland produces two related hormones, thyroxine (T4) and triiodothyronine (T3). Acting through nuclear receptors, these hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult. Disorders of the thyroid gland result primarily from autoimmune processes that either stimulate the overproduction of thyroid hormones (thyrotoxicosis) or cause glandular destruction and hormone deficiency (hypothyroidism).

THYROID GLAND

Embryological development

Thyroid is the first endocrine glandular tissue to appear in mammalian development. In humans the thyroid gland arises from two distinct regions of the endodermal pharynx. The median anlage arises from the midline of the anterior pharyngeal floor between branchial arches 1 and 2 and is visible by day 17 of gestation. In contrast, the two lateral anlage (ultimobranchial bodies) develop as caudal projections from the fourth or fifth pharyngeal pouches. The growth and descent of the median anlage is accompanied by the development of a stalk (thyroglossal duct) which keeps it attached to its pharyngeal floor origin. The subsequent obliteration of the lumen of the duct is associated with lateral

expansion of the anlage and the beginnings of the formation of the characteristic bi-lobed structure of the thyroid. Simultaneously with the descent of the median anlage, the ultimobranchial bodies separate from the pharyngeal pouches and fuse with the lateral parts of the median anlage. Degeneration of the attachments of the ultimobranchial bodies to their pharyngeal origins is accompanied by proliferation of median anlage cells which surround the tissues of the lateral anlage. This association between the median and lateral anlage is complete by the ninth week of gestation, at which stage the thyroid has its characteristic shape. The contribution of the lateral anlage tissues to the formation of functioning thyroid tissue is minimal and their main contribution is in the provision of parafollicular calcitonin-secreting (C) cells.

Structure

The thyroid gland consists of two lobes connected by an isthmus, with the adult normal gland in an iodine replete population weighing 15-20 g. The gland is attached to the anterior and lateral aspects of the trachea by loose connective tissue such that the isthmus lies just below the cricoid cartilage. The recurrent laryngeal nerves lie in the grooves between the lateral lobes and the trachea and the lateral extent of the thyroid lobes are marked by the carotid sheaths and sternocleidomastoid muscles. The well-vascularized gland is supplied by the superior and inferior thyroid arteries on each side. The gland has both adrenergic and cholinergic innervations.

The basic functional unit of the thyroid gland is the follicle. These hollow, spherical structures ranging in size from 15 to 500 µm in diameter are surrounded by a basement membrane. The wall of the unit is made up of a single layer of thyroid follicular cells, which are cuboidal when quiescent. The lumen of the follicle contains the proteinaceous colloid which is normally the major constituent of the thyroid mass and serves as the primary site of storage of thyroglobulin secreted by the thyroid follicular cells. The rich capillary network surrounding the follicles and the high blood flow through the gland ensure easy access of thyroid hormone to the circulation. Interspersed between the thyroid follicles are the parafollicular C cells which secrete calcitonin.

THYROID HORMONES

Thyroid hormone synthesis and secretion

Synthesis of adequate quantities of thyroid hormone necessitates more rapid entry of iodide into thyroid follicular cells than is possible by passive diffusion from the extracellular fluid. A poorly characterized (trapping) mechanism ensures that sufficient iodide substrate is available for hormone formation. This process is enhanced by thyroid stimulating hormone, thyrotrophin (TSH) and is responsive to the glandular content of organic iodine. The mechanism for concentrating iodide is shared by the other monovalent anions perchlorate and pertechnetate. Glandular tissue in the salivary glands and gastric

mucosa, tissues of endodermal origin, have a similar capacity for concentrating iodide.

Once iodide is trapped within the thyroid follicular cell it is rapidly oxidized in the presence of hydrogen peroxide by the enzyme thyroid peroxidase, a 933 amino acid, membrane bound, glycosylated, heme-containing protein. Oxidation is followed by the incorporation of the resulting reactive intermediate into the tyrosine residues of thyroglobulin (iodide organification). Thyroid peroxidase, which is central to this process, is predominantly localized on the apical border of the thyroid cell and this location suggests that it is at this interface between the follicular cell apical surface and the colloid that organification occurs.

Oxidation and organification of iodide result in the formation of hormonally inactive iodotyrosines (monoiodotyrosine and diiodotyrosine). The coupling of these iodinated tyrosines leads to the formation of the hormonally active iodothyronines T4 and T3. The synthesis of T4 results from the fusion of two molecules of diiodotyrosine, whereas the formation of T3 results from the coupling of a molecule of monoiodotyrosine with one of diiodotyrosine. Thyroid peroxidase plays a key role in thyroid hormone biosynthesis, not only in the catalysis of the iodination of tyrosyl residues in thyroglobulin but also in the coupling of iodotyrosyl residues in thyroglobulin to form T4 and T3.

Thyroglobulin, the main precursor of thyroid hormones is a large glycoprotein molecule present in the follicular luminal colloid in multiple forms, with the most prevalent and the major source of thyroid hormone being the 19S

molecule with a molecular size of 660 kDa. The sites in the molecule for thyroid hormone formation have been identified. There are approximately three to four T4 molecules per mole of human thyroglobulin under conditions of normal iodination, but only one in five molecules of human thyroglobulin contains a T3 residue. Thyroglobulin synthesis in the thyroid follicular cell is the same as that for other glycoproteins. Following transcription and processing of thyroglobulin mRNA and its ribosomal translation, the resulting polypeptide chain is extruded into the endoplasmic reticulum and glycosylated during transport to the Golgi apparatus. Packaging of the thyroglobulin into exocytotic vesicles in the Golgi apparatus then allows the transport of the protein in these vesicles, which also contain membrane-bound thyroid peroxidase, to the apical surface of the follicular cell, where the contents are released into the colloid-containing follicular lumen. The process of thyroglobulin biosynthesis and exocytosis is regulated by TSH.

For thyroid hormone to be secreted into the circulation, thyroglobulin from the large colloid reservoir needs to re-enter the thyroid follicular cell where it undergoes proteolytic cleavage with the release of T4 and T3, which leave the thyroid follicular cell at its basal surface to enter the capillary circulation. This process is activated by TSH with the formation of pseudopodia induced on the apical surface of the follicular cells which engulf colloid to produce colloid-containing endocytotic vesicles within the follicular cell. The subsequent fusion of enzyme-containing lysosomes with these droplets leads to the hydrolysis of thyroglobulin and the liberation of the iodotyrosines from the thyroglobulin.

REGULATION OF THYROID FUNCTION

Thyroid hormone synthesis and secretion are closely regulated by extrathyroidal (TSH) and intrathyroidal mechanisms. The thyroid participates with the hypothalamus and pituitary in a classical feedback control system. Fluctuations in hormone secretion are prevented in part by the large intraglandular store of hormone which buffers the effects of acute increases or decreases in hormone synthesis. Autoregulatory mechanisms within the gland maintain the constancy of the intraglandular hormone pool.

TSH is the major regulator of thyroid structure and function. Its secretion, in turn, is regulated by thyrotrophin releasing hormone (TRH) from the hypothalamus which stimulates the pituitary thyrotroph to release and later synthesize TSH. It is at this level in the feedback system that thyroid hormones act to inhibit function. TRH is a tripeptide synthesized by the peptidergic neurones in the supraoptic and paraventricular nuclei of the hypothalamus, and is transported from them and stored in the median eminence. Thereafter TRH enters the hypophyseal portal venous system to act on the pituitary thyrotrophs to release TSH. Although TRH and thyroid hormones are the major regulators of TSH secretion, somatostatin, dopamine, and pharmacological doses of glucocorticoids impair the release of TSH in response to TRH.

TSH is a glycoprotein hormone secreted by thyrotroph cells of the anterior pituitary. It is composed of a 14 kDa α-subunit in common with luteinizing hormone, follicle stimulating hormone and human chorionic gonadotropin, and a

specific β-subunit. It is secreted in both 1 to 2 hourly pulses and with a circadian rhythm which is characterized by a nocturnal surge which precedes the onset of sleep. By binding to the TSH receptor on the thyroid follicular cells (one of the family of seven-transmembrane spanning G-protein linked receptors), TSH activates thyroid function, predominantly through adenylate cyclase. A number of key elements of thyroid cell function have been demonstrated to be responsive to TSH stimulation; these include iodide transport with both acute and delayed effects, iodide organification, the release of thyroglobulin from exocytotic vesicles into the follicular lumen, increased pseudopod formation on the apical cell border allowing endocytosis of colloid, lysosome maturation and interaction with the endocytotic vesicle, thyroid hormone secretion, and, with chronic stimulation, hyperplasia and thyroid growth.

Autoregulatory control mechanisms are assumed to be at work when the level of TSH remains constant. In situations of TSH deficiency, variations in dietary iodine intake continue to influence iodide transport. The influence of iodine on the rate of thyroid hormone synthesis is determined by the amount and duration of administration of iodine. With increasing doses of iodide given acutely, the initial increase in the organification of iodine is then followed by a decrease. This decreasing yield of organic iodine, despite increasing dosage of iodide, is termed the acute Wolff-Chaikoff effect. As a result, synthesis of hormonally active iodothyronine is abolished and overproduction of thyroid hormone is prevented. Chronic repeated lower dose iodide administration allows

‘escape’ from this process, thus preventing the development of goitrous hypothyroidism. Pharmacological doses of iodine will, in addition, rapidly inhibit thyroid hormone release. This acute effect occurs much more rapidly than is seen with the Wolff-Chaikoff effect and the mechanism remains uncertain.

Despite the well-recognized and abundant adrenergic nerve fibre supply to the thyroid, the contribution that catecholamines make to thyroid hormone production is less well defined.

LABORATORY EVALUATION

Measurements of thyroid hormones

The techniques of measurement of thyroid hormones have moved through several eras, which began with the measurement of iodine content of serum protein (protein bound iodine) as an indirect measure of serum content of T4, evolved to competitive binding assays that use the displacement of T4 from thyroxine-binding globulin, which, in turn, have been replaced by improved immunoassays using highly specific antibodies to T4. Similar immunoassay methods have been developed for the measurement of total serum T3. Using such assay systems it is possible to establish normal ranges for circulating thyroid hormones since these hormone measurements reflect the concentrations of protein-bound hormone in the blood, they will vary with alterations in thyroid hormone binding protein concentrations. In order to overcome these problems, tests designed to measure the concentrations of free thyroid hormone levels have been

developed. Currently available assays for the assessment of free thyroid hormone which are capable of automation and therefore of handling large numbers of samples are based either on analogue methodology or methods using two-step or labelled antibody immunoassays. Recently electrochemolumences method is used to perform thyroid function tests.

The enhanced sensitivity and specificity of TSH assays have greatly improved laboratory assessment of thyroid function. Because TSH levels change dynamically in response to alterations of T4 and T3, a logical approach to thyroid testing is to first determine whether TSH is suppressed, normal, or elevated.

A normal TSH level excludes primary (but not secondary) hypothyroidism. If the TSH is elevated, an unbound T4 level is needed to confirm the presence of clinical hypothyroidism, but T4 is inferior to TSH when used as a screening test, as it will not detect subclinical or mild hypothyroidism. Circulating unbound T3 levels are normal in about 25% of patients, reflecting adaptive responses to hypothyroidism. T3 measurements are therefore not indicated.

Tests to determine the etiology of thyroid dysfunction

Once clinical or subclinical hypothyroidism is confirmed, the etiology is usually easily established by demonstrating the presence of TPO antibodies, which are present in 90 to 95% of patients with autoimmune hypothyroidism. TBII can be found in 10 to 20% of patients, but these determinations are not needed routinely. If there is any doubt about the cause of a goiter associated with

hypothyroidism, FNA biopsy can be used to confirm the presence of autoimmnune thyroiditis. Other abnormal laboratory findings in hypothyroidism may include increased creatine phosphokinase, elevated cholesterol and triglycerides, and anemia (usually normocytic or macrocytic). Except when accompanied by iron deficiency, the anemia and other abnormalities gradually resolve with thyroxine replacement

Radioiodine uptake and thyroid scanning

The only means of measuring thyroid function directly is by the use of a tracer dose of a radioactive isotope of iodine and measurement of its fractional uptake by the gland. Following the administration of an oral preparation of radiolabelled iodine, a γ-scintillation counter is used to measure radioactivity over the area of the thyroid 24 hours later, when the tracer uptake is near maximum. In patients with hyperthyroidism, uptake is likely to be higher much earlier and an additional measurement is therefore performed at 6 hours. Variations in dietary iodine intake will determine the normal range of the radioactive iodine uptake within a given population. High values do not always indicate thyroid hormone overproduction and caution is required in interpreting the result.

The efficiency of thyroid organification is examined using the discharge of radioactive iodine from the thyroid in response to the administration of potassium perchlorate. Two to three hours after an oral dose of radio-iodine, 0.5 g of potassium perchlorate is given orally in solution and its effect on radioactive

iodine uptake is assessed. In subjects with a normal organification mechanism no further uptake of radio-iodine by the thyroid occurs and less than 5 per cent of the accumulated iodide is discharged during the succeeding hour. Where an iodide organification defect exists, diffusion of iodine out of the thyroid continues and this is seen as an increased discharge of radioactivity from the thyroid gland.

Thyroid imaging

Radionuclide scanning is based on the principle that isotopically labelled materials accumulate differentially in thyroid tissue and the detection and quantification of this information is transformed into a visual display. This allows the localization of functioning and non-functioning thyroid tissue. A number of isotopes of iodine and $^{99}Tc^{m}$ pertechnetate have been used. Because pertechnetate is not organified following concentration by the thyroid gland, it diffuses rapidly out of the thyroid and this, together with its short physical half-life (6 h), makes the radiation delivered to the thyroid, by a standard dose, very low and allows imaging 20-30 min after the dose has been given. An important consideration when using pertechnetate is that some tumours of the thyroid appear to be functioning when examined by pertechnetate but are cold with radio-iodine. Improvements in scanning apparatus and in particular the development of the pinhole collimated gamma-camera (scintillation), make it possible to scan the whole thyroid without moving the camera. This method provides more rapid scanning of increased resolution.

Thyroid ultrasound

Ultrasonography of the normal thyroid produces a pattern of sparse, fine echoes in the paratracheal region. It is possible to demonstrate diffuse or localized enlargement of the gland and provide objective assessments of change in size. The sensitivity of the technique allows detection of nodules which are not clinically palpable. When these nodules are solitary the significance of their detection in this way is as yet unresolved. The major role of ultrasonography is in the differentiation of cystic from solid lesions in the thyroid and when a solitary nodule can be shown to be purely cystic this considerably reduces the likelihood of it being malignant.

The demonstration by radio-isotope scanning of a solitary cold nodule, which is then shown by ultrasonography to be solid, demands further investigation. The use in this setting of fine-needle aspiration biopsy coupled with cytological examination provides a simple, safe, and rapid means for diagnosis and significantly reduces the need for referral for surgical investigation and removal.

Peripheral effects of thyroid hormones

In theory a good test of whether a patient's tissues are being exposed to too much or too little thyroid hormone would not be a measurement of circulating hormone concentrations but rather a measure of the direct effects of thyroid hormones on peripheral tissues. Unfortunately no simple, reproducible, specific,

and sensitive test of such effects is available. Such a measure, would be of particular value in patients without clinical and biochemical evidence of hyperthyroidism but in whom a subnormal TSH or an absent TSH response to TRH suggests subnormal thyroid function. In this group of patients two subgroups can be discriminated: those in whom the decision concerns whether or not treatment of subclinical hypothyroidism might result in benefit, and, in contrast, those on replacement thyroxine in whom concerns about over treatment could then be more directly addressed.

Further groups of patients in whom such an approach might contribute to management are those presenting with mild hypothyroidism in whom biochemical parameters have not been decisively helpful, others with thyroid hormone resistance, and those with non-thyroidal illness (the sick euthyroid syndrome). In these settings the best established and validated (but also most cumbersome) investigation is the basal metabolic rate; the calorigenic effect of thyroid hormones increases energy expenditure and heat production. Since heat production cannot be measured directly, the test measures oxygen consumption converted into an energy equivalent and then related to body surface area. Other tests make use of the relationship between muscle relaxation after a contraction and thyroid status by measuring the speed of relaxation of the Achilles tendon reflex, which is prolonged in hypothyroidism and shortened in hyperthyroidism.

Tests of myocardial contractility have also been developed and the best validated is the measurement of the interval between the initiation of the QRS

complex on the electrocardiogram and the arrival of the pulse wave in the brachial artery at diastolic pressure (QKd). This is shortened in hyperthyroidism and prolonged in hypothyroidism. All three of these measures are altered by a number of non-thyroidal states, so that they can only be interpreted with circumspection. The serum cholesterol is usually elevated in hypothyroidism and decreased in hyperthyroidism and the serum creatinine phosphokinase may be increased in the hypothyroid state. It is suggested that absent serum sex hormone binding globulin and absent serum ferritin responses to administered thyroxine are likely to be associated with generalized resistance to thyroid hormone.

HYPOTHYROIDISM

Many structural or functional abnormalities can impair the production of thyroid hormones and cause the clinical state termed hypothyroidism.

CAUSES OF HYPOTHYROIDISM

Primary hypothyroidism with Goiter

Acquired

- Hashimoto's thyroiditis (autoimmune thyroiditis type 2)
- Iodine deficiency (endemic goiter)
- Drugs blocking synthesis or release of T4 (lithium, iodide, sulfonamides)
- Goitrogens in foodstuffs
- Cytokines (interferon α, interleukin-2)
- Thyroid infiltration (amyloidosis, hemochromatosis, sarcoidosis, etc.)

Congenital

- Iodide transport or utilization defect
- Iodotyrosine dehalogenase deficiency
- Organification disorders (Thyroid peroxidase deficiency)
- Defects in thyroglobulin synthesis or processing

Atrophic Hypothyroidism

Acquired

Hashimoto's disease (autoimmune thyroiditis type 2B)

Postablative due to ^{131}I, surgery or irradiation

Congenital

Thyroid agenesis

TSH receptor defects

Thyroidal Gs protein abnormalities

Idiopathic TSH unresponsiveness

Transient Hypothyroidism

Following subacute, painless, or post partum thyroiditis

Consumptive Hypothyroidism

Rapid destruction of thyroid hormone due to D3 expression in large hemangiomas of hemangioendotheliomas

Central hypothyroidism

Acquired

Pituitary origin (secondary)

Hypothalamic disorders (tertiary)

Dopamine and severe illness

Congenital

TSH deficiency

TSH receptor defect

Resistance to thyroid hormone

Generalized

Pituitary dominant

EPIDEMIOLOGY

Primary hypothyroidism accounts for approximately 99% of cases, with fewer than 1% being due to TSH deficiency.

Clinically apparent acquired impairment of thyroid function affects about 2% of adult women and about 0.1 to 0.2% of adult men[7,25]. Subclinical hypothyroidism, an elevated TSH level in an asymptomatic patient, affects 1 to 10% of adult population, with the highest rate approaching 26% in elderly women[6,10,11]. Neonatal screening programs for congenital hypothyroidism discover hypothyroidism in almost 1 in 3500 newborns[26].

CLINICAL PRESENTATION

Hypothyroidism can affect all organ systems, and these manifestations are largely independent of the underlying disorder but are a function of the degree of hormone deficiency.

Skin and Appendages

Hypothyroidism causes an accumulation of hyaluronic acid that alters the composition of the ground substance in the dermis and other tissues. This material is hygroscopic, producing the mucinous edema that is responsible for the thickened features and puffy appearance (myxedema) with full-blown hypothyroidism. Myxedematous tissue is characteristically boggy and nonpitting and is apparent around the eyes, on the dorsa of the hands and feet, and in the supraclavicular fossae. It causes enlargement of the tongue and thickening of the pharyngeal and laryngeal mucous membranes.

The secretions of the sweat glands and sebaceous glands are reduced, leading to dryness and coarseness of the skin, which in extreme cases may resemble icthyosis.

Easy bruising occurs due to an increase in capillary fragility. Head and body hair becomes dry and brittle, lacks lusterness, and tends to fall out.

Cardiovascular System

The cardiac output at rest is decreased because of reduction in both stroke volume and heart rate, reflecting loss of the inotropic and chronotropic effects of thyroid hormones. Peripheral vascular resistance at rest is increased, and blood volume is reduced. These hemodynamic alterations cause narrowing of pulse pressure, prolongation of circulation time, and decrease in blood flow to

tissues[27,28]. The decrease in cutaneous circulation is responsible for the coolness and pallor of the skin and sensitivity to cold.

In severe primary hypothyroidism the cardiac silhouette is enlarged, and the heart sounds are diminished in intensity. These findings are the result largely of effusion into the pericardial sac of fluid rich in protein and glycosaminoglycans, but the "flabby" myocardium may also be dilated [27].

Angina pectoris is uncommon, but it may appear or worsen during treatment of the hypothyroid state with thyroid hormone[27,29,30]. There is considerable controversy over whether hypothyroidism is a risk factor for atherosclerosis. The Whickham Study[7] showed no increase in cardiovascular mortality in patients with subclinical hypothyroidism over 20 years, whereas the Rotterdam Study[11] suggested that there was a twofold increase in risk. Systemic vascular resistance is increased, and hypertension is more common[31].

Electrocardiographic changes include sinus bradycardia, prolongation of the PR interval, low amplitude of the P wave and QRS complex, alterations of ST segment, and flattened or inverted T waves. Pericardial effusion is probably responsible for the low amplitude in severe hypothyroidism. Rarely, complete heart block may be present, but this disappears when hypothyroidism is treated[28].

Serum levels of homocysteine, creatine kinase, aspartate aminotransferase and lactate dehydrogenase may be increased.

The combination of large heart, hemodynamic and electrocardiographic alterations, and the serum enzyme changes has been termed *myxedema heart.*

Myxedema heart rarely causes heart failure by itself because the usual hemodynamic response to exercise in hypothyroidism is typically normal, although exceptions have been reported[27,28].

Respiratory System

Pleural effusions usually are evident only on radiological examination but in rare instances may cause dyspnea. Lung volumes are usually normal, but maximal breathing capacity and diffusing capacity are reduced.

Obstructive sleep apnea is common but is reversible with restoration of a euthyroid state.

Alimentary System

Although most patients experience a modest gain in weight, appetite is usually reduced. The weight gain that occurs is caused partly by retention of fluid by the hydrophilic glycoprotein deposits in the tissues. Peristaltic activity is decreased and, together with the decreased food intake, is responsible for the frequent complaint of constipation.

Central and Peripheral Nervous System

Thyroid hormone is essential for the development of the central nervous system. Deficiency in fetal life or at birth causes retention of the infantile characteristics of the brain. If the deficiency is not corrected in early postnatal life,

the damage is irreversible. Deficiency of thyroid hormone beginning in adult life causes less severe manifestations that usually respond to treatment with the hormone.

All intellectual functions, including speech, are slowed. Loss of initiative is present, slow-wittedness and memory defects are common, lethargy and somnolence are prominent, and dementia in elderly patients may be mistaken for senile dementia. Psychiatric disorders are common and are usually of the paranoid or depressive type and may induce agitation (myxedema madness)[32,33].Epileptic seizures have been reported and tend to occur in myxedema coma.

Thick, slurred speech and hoarseness are due to myxedematous infiltration of the tongue and larynx, respectively. Body movements are slow and clumsy, and cerebellar ataxia may occur.

Numbness and tingling of the extremities are frequent; in the fingers theses symptoms may be due to compression by glycosaminoglycan deposits in and around the median nerve in the carpal tunnel (carpal tunnel syndrome)[34,35]. The tendon reflexes are slow, especially during the relaxation phase, producing the characteristic “hung-up reflexes”; this phenomenon is due to a decrease in the rate of muscle contraction and relaxation rather than a delay in nerve conduction.

Muscular System

Stiffness and aching of muscles are common and are worsened by cold temperatures. Delayed muscle contraction and relaxation cause the slowness of

movement and delayed tendon jerks. Muscle mass may be reduced or enlarged due to interstitial myxedema.

Skeletal System

Thyroid hormone is essential for normal growth and maturation of the skeleton, and growth failure is due both to impaired general protein synthesis and to a reduction in growth hormone, but especially of insulin-like growth factor I. before puberty, thyroid hormone plays a major role in the maturation of bone. Deficiency of thyroid hormone in early life leads to both a delay in the development of, and an abnormal, stippled appearance of the epiphyseal centers of ossification (epiphyseal dysgenesis). Impairment of linear growth leads to dwarfism in which the limbs are disproportionately short in relation to the trunk but cartilage growth is unaffected.

Levels of calcium and phosphorus in serum are usually normal, but calcium may be slightly elevated

Renal Function

Renal blood flow, glomerular filtration rate, and tubular reabsorptive and secretory maxima are reduced. Blood urea nitrogen and serum creatinine levels are normal, but uric acid levels may be increased.

The impaired renal excretion of water and retention of water by the hydrophilic deposits in the tissues result in an increase in total body water, even though plasma volume is reduced.

Hematopoietic System

In response to the diminished oxygen requirements and decreased production of erythropoietin, the red blood cell mass is decreased; this is evident in the mild normocytic, normochromic anemia that often occurs.

The total and differential white blood cell counts are usually normal, and platelets are adequate.

Pituitary and Adrenocortical Function

Patients with severe hypothyroidism may have increased serum prolactin levels that correlate with the level of serum TSH, and galactorrhea may develop in some patients. Treatment with thyroid hormone corrects serum prolactin and TSH levels and causes disappearance of galactorrhea, if present. The cause of hyperprolactinemia in hypothyroidism is uncertain but may result from enhanced sensitivity of the lactotropes to TSH.

In severe, long-standing primary hypothyroidism, pituitary and adrenal function may be secondarily decreased and adrenal insufficiency may be precipitated by stress or by rapid replacement therapy with thyroid hormone.

Reproductive Function

In adult women, severe hypothyroidism may be associated with diminished libido and failure of ovulation. Fertility is reduced, and spontaneous abortion may result, although many pregnancies are successful. Hypothyroidism in men may cause diminished libido, impotence, and oligospermia.

Secretion of progesterone is inadequate and endometrial proliferation persists, resulting in excessive and irregular breakthrough menstrual bleeding. These changes may be due to deficient secretion of luteinizing hormone. Rarely, in primary hypothyroidism, secondary depression of pituitary function may lead to ovarian atrophy and amenorrhea.

Energy Metabolism

The decrease in energy metabolism and heat production is reflected in the low basal metabolic rate, decreased appetite, cold intolerance, and slightly low basal body temperature. Both the synthesis and degradation of protein are decreased, the latter especially so, with the result that nitrogen balance is usually slightly positive. The decrease in protein synthesis is reflected in retardation of both skeletal and soft tissue growth.

The oral glucose tolerance curve is characteristically flat, and the insulin response to glucose is delayed. These alterations may be due to a decreased rate of absorption of glucose from gut. Degradation of insulin is slow, so the sensitivity to exogenous insulin may be decreased. Increased insulin sensitivity and decrease in

appetite presumably account for the decrease in insulin requirement when hypothyroidism develops in a patient with preexisting diabetes mellitus. Hepatic glycolysis is unaffected by hypothyroidism.

Both the synthesis and degradation of lipid are depressed, the latter especially so, the net effect being one of lipid accumulation, especially of low-density lipoprotein (LDL) and triglycerides. High-density lipoprotein (HDL) concentrations are reduced. The increase in serum cholesterol in primary (but not central) hypothyroidism is accompanied by increased levels of serum phospholipids, serum triglycerides, and LDL.

The features described above are the consequence of thyroid hormone deficiency. However, autoimmune hypothyroidism may be associated with signs and symptoms of other autoimmune diseases, particularly vitiligo, pernicious anemia, Addison disease, alopecia areata, and type 1 diabetes meelitus. Less common associations include celiac disease, dermatitis herpetiformis, chronic active hepatitis, rheumatoid arthritis, systemic lupus erythematousus, and Sjögrens's syndrome. Thyroid associated ophthalmopathy, which usually occurs in Grave's disease, occurs in about 5% of patients with autoimmune hypothyroidism.

TREATMENT

If there is no residual thyroid function, the daily replacement dose of levothyroxine is usually 1.6 µg/kg body weight (typically 100 to 150 µg). In many patients, however, lower doses suffice until residual thyroid tissue is destroyed.

Adult patients under 60 years without evidence of heart disease may be started on 50 to 100 µg levothyroxine (T4) daily. The dose is adjusted on the basis of TSH levels, with the goal of treatment being a normal TSH, ideally in the lower half of the reference range. TSH responses are gradual and should be measured about 2 months after instituting treatment or after any subsequent change in levothyroxine dosage. The clinical effects of levothyroxine replacement are often slow to appear. Patients may not experience full relief from symptoms until 3 to 6 months after normal TSH levels are restored. Adjustment of levethyroxine dosage is made in 12.5 or 25 µg increments if the TSH is high; decrements of the same magnitude should be made if the TSH is suppressed.

Particular care is needed in beginning treatment in the elderly and in those with a history of heart disease. In patients with coronary artery disease low levels of circulating thyroid hormone may protect the heart against increased demands that would otherwise result in increasing angina. In such patients appropriate therapy for their coronary artery disease should be considered before beginning thyroxine. When thyroxine is given, it should be begun at a low dose (25 µg daily or on alternate days) and be increased cautiously every 4 weeks until euthyroidism is achieved.

Once full replacement is achieved and TSH levels are stable, follow-up measurement of TSH is recommended at annual intervals and may be extended to every 2 to 3 years, if a normal TSH is maintained over several years.

MYXEDEMA COMA

Myxedema coma is an uncommon complication of long-standing hypothyroidism and is typically seen in the elderly, often precipitated by severe infection, therapy with sedative agents, or by inadequate heating during cold weather. It has a high mortality. It is characteristically associated with depression of the level of consciousness, and hypothermia. Alveolar hypoventilation leading to carbon dioxide retention and a dilutional hyponatremia are often seen.

Early recognition of the condition and its management are essential. The latter is complicated by the sluggish circulation and hypometabolism. General supportive measures include intravenous fluids, antibiotics, ventilation, and slow rewarming. Thyroid hormone replacement is best given as an intravenous bolus of 100 µg of T3, because of its rapid action. Thereafter a reasonable dose is 20 µg three times a day. It is worth covering the initial treatment period with hydrocortisone (100 mg daily) to protect against the possibility of associated adrenocortical insufficiency.

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is defined as an isolated elevated serum thyrotrophin level in the setting of normal serum thyroid hormone levels, in the presence or absence of symptoms[4].

Although subclinical hypothyroidism is the term most frequently used to describe this condition and will be used in this discussion, it is not necessarily apt, since on close questioning many patients disclose mild, nonspecific symptoms. Mild hypothyroidism may be more appropriate term for this very common syndrome.

The findings of slightly elevated TSH and normal thyroid hormone levels do not necessarily imply the presence of subclinical hypothyroidism. Several medications and conditions are known to cause an elevation in TSH. Some drugs such as sulfonylureas, lithium, amiodarone, ethionamide, phenylbutazone, aminoglutethimide, and iodine can interfere with thyroid hormone production or release and secondarily result in a slight elevation of TSH. In addition, dopamine antagonist such as metoclopromide and domperidone may cause exaggerated TSH response to TRH stimulation by altering the inhibitory effect of dopamine on TSH secretion. Furosemide has also been shown to increase levels of TSH, especially in recovering critically ill patients. Other conditions that cause elevated TSH include thyroid hormone resistance, thyroid hormone secreting tumors (both should be

associated with high free thyroxine level), psychiatric illness, adrenal insufficiency, renal failure, hyperprolactinemia and systemic illness[36].

PREVALANCE AND NATURAL HISTORY

Large population studies have suggested that the prevalence of subclinical hypothyroidism is much higher in women than men and increases with age. In the Whickham survey, TSH levels above 6mIU/l were approximately three times more common in females (7.5%) than in males (2.8%) and occurred more frequently in females over 45 years of age. TSH levels also showed a progressive increase with age in women but not in men[37].

The overall prevalence has been reported to range from 4–10% in large general population screening surveys and from 7–26% in studies of the elderly. Most studies have shown that subclinical hypothyroidism is more frequent in the female sex. A recent study demonstrated a prevalence of elevated TSH in 16% of men and 21% of women over age 74 years[10,38,39].

In patients found to have an elevated TSH level, approximately 75% have values lower than 10 mIU/L[38]. Of patients with subclinical hypothyroidism, approximately 2% to 5% per year will progress to overt hypothyroidism. Overt hypothyroidism is generally defined as a low serum FT_4 concentration with elevated serum TSH concentration[6], but in some cases individuals with hypothyroid symptoms and high TSH (>10 mIU/L) with low normal FT_4 have been among those defined as having overt hypothyroidism[7]. The rate of

progression is proportional to the baseline serum TSH concentration and is higher in individuals with antithyroid antibodies[7]. There is also a strong association between positive antithyroid antibodies and elevated TSH. Generally the prevalence of elevated TSH levels parallels that of antibody positivity[37]. A high prevalence of antibodies was found in a UK study where antibodies were present in 81% of those with TSH concentration over 10 mU/l, 46% of those with TSH over 5 mU/l and less than or equal to 10 mU/l and only in 5.7% of those whose TSH concentration was less than 0.5 mU/l[6]. Interestingly, the NHANES III survey found a significant association between anti-thyroid peroxidase antibody with hypo- or hyperthyroidism but not thyroglobulin antibody.

After 20 years of follow-up of subjects in the Whickham Survey, the risk of overt hypothyroidism was found to be 4.3% per year in women with elevated TSH and antithyroid antibodies at baseline. This is a 38 times increased risk over normal women. Moreover, an isolated elevation in TSH or presence of antithyroid antibodies alone at baseline also conferred an increased risk of overt hypothyroidism (2.6% per year and 2.1%per year respectively)[7]. Progression to hypothyroidism was noted to be more common in those with initial TSH value greater than 10 mU/l and in those with positive anti-thyroid antibodies[6]. Huber et al found that basal TSH, thyroid reserve (increase in T3 after TRH stimulation) and the presence of antimicrosomal antibody are important prognostic factors for the development of overt hypothyroidism. Interestingly, antibodies against thyroglobulin did not have a predictive value.

EFFECTS ON SERUM LIPID LEVELS

The relationship between mild thyroid failure and reversible elevation in serum lipid levels has been widely investigated, but the findings remain controversial. Several cross-sectional studies suggest that serum cholesterol concentrations are elevated in individuals with mild thyroid failure when compared with euthyroid controls[40]. In other similar studies, however, the observed differences between euthyroid and mild hypothyroid individuals have not been significant [41].

The Colorado study which screened 25,862 subjects found that mean total cholesterol and low density lipoprotein cholesterol progressively increased with increasing serum TSH levels[38]. A reanalysis by Tanis et al in 1996 found that subclinical hypothyroidism was two to three times more frequent in people with elevated total plasma cholesterol.

Thyroid substitution therapy restoring the TSH levels to normal decreased total cholesterol by 0.2 to 0.4 mmol/l and mean LDL cholesterol by 0.26mmol/l and increased in HDL cholesterol by 0.08 mmol/l while triglycerides, and apolipoprotein AI levels remained unchanged. In another study, total cholesterol and LDL cholesterol levels decreased only in pretreatment TSH values greater than 10 mU/l[42]. The decrease in total cholesterol and LDL levels with pretreatment TSH values greater than 40 mU/l was greater than in those levels between 10 and 40 mU/l.

CARDIAC EFFECTS

Cardiac changes are evident in subclinical hypothyroidism. These include impairment of left ventricular diastolic function at rest (affecting the relaxation of the left ventricle and hence ventricular filling), reduced LV systolic function, prolongation of pre-ejection time and lastly, impaired intrinsic myocardial contractility. There is evidence that these abnormalities improve with L-T4 treatment, demonstrating that adequate thyroid replacement improves cardiac output accompanied by substantial decrease in systemic vascular resistance, a reversal of diastolic dysfunction, and importantly an improvement in left ventricular ejection fraction during exercise. It has been demonstrated in the Rotterdam Study that subclinical hypothyroidism is a strong indicator risk for atherosclerosis and myocardial infarction[11].

Inadequately treated hypothyroidism has also been demonstrated to have angiographic evidence of coronary atherosclerosis progression. Impairment of endothelium-dependent vasodilatation, a harbinger of atherosclerosis, has also been detected in patients with subclinical hypothyroidism which can be reversed by levothyroxine supplementation.

In view of clear structural and biological cardiovascular risks associated with the presence of subclinical hypothyroidism, treatment of this condition would be expected to provide protection against the development of cardiovascular disease, although there have been no long term outcome studies published to date.

SOMATIC AND NEUROMUSCULAR EFFECTS

Patients with subclinical hypothyroidism can have subtle clinical manifestations and non-specific symptomatology such as dry skin, cold intolerance, constipation, and easy fatigability. In addition, patients with muscular symptoms have mitochondrial oxidative dysfunction with significant lactate increment during exercise. Misiunas et al also demonstrated the presence of subclinical polyneuropathy of probable axonal origin in patients with subclinical hypothyroidism[43].

Subclinical hypothyroid subjects reported significantly more total symptoms than euthyroid individual in the Colarado study[38] and these symptoms do improve with L-T4 therapy. The greatest improvement seen is of patients with baseline TSH of >12 mU/l. Kong et al observed no improvement in symptoms score after trial of thyroxine for six months in patients with TSH level between 5 and 10 mU/l[44].

Prospective studies suggest that patients with mild thyroid failure have a higher prevalence of somatic symptoms, mood disorders, cognitive dysfunction, and atypical responses to standard psychiatric therapeutic interventions[4]. The lifetime frequency of depression is significantly higher in patients with subclinical hypothyroidism compared with patients with normal thyroid function, suggesting that subclinical hypothyroidism lowers the threshold for depression.

TREATMENT

Risks and benefits of treatment

Among patients with untreated subclinical hypothyroidism, there is no single level of serum TSH at which clinical action is always either indicated or contraindicated. As the serum TSH concentration increases above 10 mIU/L, however, the basis for initiating treatment is more compelling. Clinical context is particularly important. This opinion reflects clinical experience and judgment as well as the literature that suggests improvement in symptoms and possible lowering of LDL cholesterol. There are no studies that demonstrate decreased morbidity or mortality with treatment. The potential risks of therapy are limited to the development of subclinical hyperthyroidism, which may occur in 14% to 21% of individuals treated with levothyroxine.

Subclinical Hypothyroidism with Serum TSH of 4.5 to 10 mIU/L.

Although some studies suggest an association between subclinical hypothyroidism and systemic hypothyroid symptoms[38] or cardiac dysfunction[15], others do not. The available data do not confirm clear-cut benefits for early therapy compared with treatment when symptoms or overt hypothyroidism develop[44]. Therefore, routine levothyroxine treatment for patients with TSH levels between 4.5 and 10 mIU/L is not recommended, but thyroid function tests should be repeated at 6- to 12-month intervals to monitor for improvement or worsening in TSH level.

Subclinical Hypothyroidism with Serum TSH Higher Than 10 mIU/L

Levothyroxine therapy is reasonable for patients with subclinical hypothyroidism and serum TSH higher than 10 mIU/L. The rate of progression is 5% in comparison with patients with lower levels of TSH, and treatment may potentially prevent the manifestations and consequences of hypothyroidism in those patients who do progress. Still, the evidence that therapy will reduce total and LDL cholesterol levels and improve symptoms in these patients is inconclusive.

Subclinical Hypothyroidism During Pregnancy

Pregnant women or women of childbearing potential planning to become pregnant who are found to have elevated serum TSH should be treated with levothyroxine to restore the serum TSH concentration to the reference range. This recommendation is based on the possible association between high TSH and either increased fetal wastage or subsequent neuropsychological complications occurring in the offspring due to thyroid insufficiency. Although there are no published intervention trials assessing the benefits of thyroid hormone replacement in this special population, the potential benefit-risk ratio of levothyroxine therapy justifies its use. It is important to note that the requirement for levothyroxine in treated hypothyroid women frequently increases during pregnancy. Therefore, serum TSH concentration should be monitored every 6 to 8 weeks during pregnancy and the

levothyroxine dose modified as needed. The risks of appropriately managed levothyroxine therapy in pregnancy are minimal.

Subclinical Hypothyroidism in Treated Overt Hypothyroid Individuals

When subclinical hypothyroidism is noted in levothyroxine-treated patients with overt hypothyroidism, the dosage of levothyroxine should be adjusted to bring the serum TSH into the reference range. Whether the target TSH level should be in the lower half of the reference range is controversial because there are no data demonstrating improved clinical outcomes with this strategy. Nevertheless, when the serum TSH is in the upper half of the reference range and levothyroxine-treated patients continue to note symptoms suggestive of hypothyroidism, it is reasonable to increase the levothyroxine dosage to bring the serum TSH into the lower portion of the reference range. The rapidity of the dosage adjustment depends on the patient's age and medical comorbidities. Minimal TSH elevations may not require dosage adjustment in patients who feel well, particularly those with arrhythmias or other cardiac disorders.

To conclude, the patients with serum TSH greater 10mU/l should be treated with thyroxine. The AACE has recommended treatment in patients with TSH levels between 5 and 10 mU/l in conjunction with a goiter or positive anti-thyroid peroxidase antibodies or both and also in the presence of symptoms. If the patients are antibody negative and TSH levels are between 5 and 10 mU/l, then an annual

check of serum TSH is recommended, with commencement of T4 once the serum TSH rises above 10 mU/l.

Arguments against Treatment

The arguments against treatment are its expense and the likelihood that some, or even most, patients will not benefit. There is also a danger of overtreatment, which could cause iatrogenic hyperthyroidism and ultimately lead to more serious abnormalities (e.g., osteopenia and atrial fibrillation) than leaving the subclinical hypothyroidism untreated. Indeed, in one large study, suppressed serum thyrotrophin levels consistent with the occurrence of overtreatment were found in 21 percent of patients who were taking thyroid hormone[38].

THYROXINE THERAPY

Given the high rate of conversion of subclinical hypothyroidism to overt hypothyroidism in the presence of circulating antithyroid antibodies, it makes sense to treat asymptomatic persons with positive antibody tests even if they have normal serum lipid levels. However, because an elevated serum thyrotrophin level is associated with an increased risk of overt hypothyroidism even in the absence of antithyroid antibodies, positive antithyroid-antibody titers should not be the sole criterion for therapy. It is also reasonable to treat subclinical hypothyroidism in pregnant women and in women who have ovulatory dysfunction with infertility.

A therapeutic trial for subclinical hypothyroidism is warranted if patients have symptoms consistent with the presence of mild hypothyroidism, hypercholesterolemia, or a goiter. Although the overlap in symptoms between patients with subclinical hypothyroidism and euthyroid persons makes it difficult to predict who will have a response to treatment, some patients have a remarkable improvement in their symptoms with thyroxine therapy. The positive findings in some small clinical trials[45,46] also support the use of therapy in symptomatic patients, and thyroxine replacement can always be discontinued if there is no apparent benefit.

An initial dose of thyroxine of 0.05 to 0.075 mg per day is usually sufficient to normalize the serum thyrotrophin level. Patients with coronary artery disease should receive lower initial doses (e.g., 0.0125 to 0.025 mg daily). Serum thyrotrophin levels should be measured four to six weeks after therapy is begun, after any change in the dose, and then annually once the levels become stable. Thyroxine requirements may increase over time if there is progressive thyroid failure. Once an elevated serum thyrotrophin level is detected and confirmed, the costs of annual follow-up with clinical assessment and laboratory testing are relatively similar whether or not patients are treated with thyroxine. Without treatment, only 5 percent of elevated serum thyrotrophin levels will revert to normal values one year later in older persons. The evidence supports the use of treatment for most patients, as long as therapy is monitored with the use of annual measurements of serum thyrotrophin.

MATERIALS AND METHODS

Case selection

Women above the age of 50 years attending the Medical outpatient clinic at Stanley Medical College and Hospital, Chennai, from June 2005 to December 2005 were studied. A sample of 140 women was randomly selected. All the participating women were examined for thyroid function. Women with subclinical hypothyroidism (defined as TSH > 5.5 μIU/ml with normal free T4 and free T3) were considered as cases, and women without subclinical hypothyroidism were considered as controls. Laboratory measurements and clinical assessments were carried out on all the participants.

Exclusion criteria

Those with

- Known thyroid disease
- History of neck irradiation
- Chronic renal failure
- Severe illness (such as infection, recent myocardial infarction, severe heart failure, or recent intensive care admission)
- Taking pharmaceuticals such as beta-blockers, amiodarone, interferon-α

were excluded.

Measurements

Thyroid function test - Free T4, free T3, and TSH levels were measured. Thyroid function test is done using the electrochemolumences method. The normal range for TSH is 0.30-5.50 µIU/ml, for free T4 the normal range is 0.70-1.80 ng/dL, and for free T3 it is1.70-4.20 pg/ml.

Clinical assessments

Participants with subclinical hypothyroidism were examined for the presence of goiter and symptoms of hypothyroidism.

Analytical methods

The following data were collected from the entire study group:

- Age
- Presence of Hypertension (defined as BP >140/90 mmHg on more than one occasion, or the patient is known to be hypertensive)
- Diabetes mellitus (defined as fasting blood sugar >126 mg% on two consecutive readings one month apart, or the patient is known to be diabetic)
- Ischemic heart disease (defined as angina or myocardial infarction by self report or by analysis of a standard 12 lead ECG)

Comparison between cases with subclinical hypothyroidism and normal control subjects of similar age and ethnic group was done with regard to the presence of IHD, hypertension, and diabetes mellitus.

Statistical analysis

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS). Different statistical methods were used as appropriate. Mean ±SD was determined for quantitative data and frequency for categorical variables. The independent t-test was performed on all continuous variables. The normal distribution of the data was checked before any t-test. The Chi-Square test was used to analyze group difference for categorical variables. In logistic regression models, age was adjusted for the estimation of each or all the independent effects of hypertension, ischemic heart disease, and diabetes. A p-value <0.05 was considered significant.

RESULTS

140 women above the age of 50 years who visited the Medical outpatient clinic during the study period were studied.

41 women were found to have the criteria set for the definition of subclinical hypothyroidism, which meant a rate of 29.2%. Patients with subclinical hypothyroidism were regarded as cases and the remaining 99 patients were the control group.

There were differences in the mean age distribution among cases and controls. The mean age for patients with subclinical hypothyroidism was 64.7±8.1 years. The mean age for controls was 63.1±8.8 years.

The age distribution of patients (Fig. 1) with subclinical hypothyroidism and controls are shown in table 1.

Table 1

Age Distribution

Age in years	Patients with SH [Cases (Total=41)]	Patients without SH [Controls (Total=99)]
50 – 59	**13**	**41**
60 – 69	**15**	**33**
70 and above	**13**	**25**

(SH = Subclinical hypothyroidism)

There were 54 patients in the age group of 50-59 yrs, of which 13 (24%) were subclinical hypothyroid patients. In the 60-69 age group there were 48 patients. The number of subclinical hypothyroid patients were 15 (31.2%). In above 70 age group there were 38 patients, of which 13 (34.2%) were having subclinical hypothyroidism.

The mean TSH level in patients with subclinical hypothyroidism was 11.82 µIU/ml (Range: 5.81-31.38). For FT4 it was 1.02 ng/dl (Range: 0.72-1.64) and for FT3 its 2.63 pg/ml (Range: 1.82-4.02). This is shown in table 2.

Table 2

	Mean	**Range**
TSH (µIU/ml)	**11.82**	**5.81-31.38**
FT4 (ng/dl)	**1.02**	**0.72-1.64**
FT3 (pg/ml)	**2.63**	**1.82-4.02**

(FT3 = Free T3, FT4 = Free T4, TSH = Thyroid Stimulating Hormone)

There were 41 patients with TSH level more than 5.5 µIU/ml, the upper level of normal range (0.30-5.5 µIU/ml). They are the subclinical hypothyroid patients in this study. Of those 41 patients, 25 (61%) had TSH level between 5.5 to 10 µIU/ml. The remaining 16 (39%) patients had TSH level more than 10 µIU/ml.

The following table shows the TSH levels in patients with subclinical hypothyroidism (Fig. 2).

Table 3

TSH Levels in Patients with Subclinical Hypothyroidism

TSH level in µIU/ml	No. of patients (%) Total no. = 41
5.5-10	25 (61%)
>10	16 (39%)

Hypothyroid symptoms (fig. 3) were reported in 12 of 41 (29%) patients with subclinical hypothyroidism. Fatigability was the most common complaint, followed by weight gain and constipation, these rates being 10 (24%), 8 (19.5%) and 7 (17%) respectively. Other complaints like cold intolerance and infertility were less commonly reported.

Table 4

Frequency of Hypothyroid Symptoms in Patients with SH

Fatigability	10 (24%)
Weight gain	8 (19.5%)
Constipation	7 (17%)
Others (Cold intol., Infertility, etc)	8 (19.5%)

Goiter was present in 8 out of 41 patients (Fig. 4) with subclinical hypothyroidism (19.5%) and 9 out of 99 patients without subclinical hypothyroidism (9%).

The incidence of risk factors like hypertension, diabetes and ischemic heart disease were compared between patients with subclinical hypothyroidism and controls (Fig. 5). They were analyzed independently with Chi-Square test. The p-values showed that patients with subclinical hypothyroidism were significantly associated with ischemic heart disease compared to controls. The p-value is not significant for hypertension and diabetes. This is shown in the table below.

Table 5

	Patients with SH		**Patients without SH**		**p-value**
	N	**%**	**N**	**%**	
HT	**11**	**26.8%**	**25**	**25.3%**	**0.85**
DM	**9**	**22.0%**	**21**	**21.2%**	**0.93**
IHD	**9**	**22.0%**	**9**	**9.1%**	**0.04**

After taking all the above risk factors into consideration in multiple regression, p-value is still significant for ischemic heart disease alone. This is shown in the following table.

Table 6

	Odd Ratio	95% Confidence Interval		p - value
		Lower	Upper	
HT	**1.162**	**0.496**	**2.722**	**0.730**
DM	**0.676**	**0.246**	**1.862**	**0.449**
IHD	**3.398**	**1.101**	**10.493**	**0.033**

DISCUSSION

Subclinical hypothyroidism is highly prevalent in elderly women. A prevalence of 11–26% had been reported in previous studies[6, 12, 38, 47], while our study showed that 29.2% of the elderly women above the age of 50 years attending the outpatient clinic had subclinical hypothyroidism. This higher prevalence in our population could be due to environmental or genetic factors, which should be verified in further studies.

Surveys that stratified TSH levels indicate a predominance of TSH <10 µIU/ml, which accounts for 55–85% of cases[5,7,48]. Almost 61% of our patients with subclinical hypothyroidism had TSH <10 µIU/ml. Studies that have reported thyroid antibody test on subjects with elevated TSH demonstrated seropositivity rates from 20–78%[6,9,10,49.]

Goiter is twice as prevalent among patients with subclinical hypothyroidism[10]. It is found in 19.5% of our patients with subclinical hypothyroidism as against 9% in controls.

Several studies have suggested that mild symptoms of hypothyroidism are more prevalent in patients with subclinical hypothyroidism than in age-matched controls[38,49]; fatigability and weight gain were the most frequent[44], but not all studies have found this to be true[51]. Twenty-nine percent of our patients with subclinical hypothyroidism had symptoms, fatigability being the most common.

There have been three published randomized prospective placebo-controlled trials on the therapy of symptoms in patients with subclinical hypothyroidism[45,52,53]. Two trials reported significant improvement in the symptoms of hypothyroidism, whereas the third found no benefit of therapy[45,52,53]. The benefit of therapy was related to TSH level, being more in those whose mean serum TSH was 12.7 mU/l at base line[52]. In women with SH and ovulatory dysfunction, thyroxine therapy may restore fertility[54].

Case control and cross-sectional studies on the association between subclinical hypothyroidism and cardiovascular diseases have been done, but results were controversial[10,12,18,55-57]. A 20- year follow-up study of the original Whickham survey[58] showed no association between elevated TSH and increased risk of IHD, while a report of 1149 women from Rotterdam showed increased atherosclerotic vascular disease and myocardial infarction in patients with subclinical hypothyroidism[12]. The present study showed a significant increase in IHD in patients with subclinical hypothyroidism compared with controls (P value 0.033). Several studies on the association between subclinical hypothyroidism and dyslipidemia have been done. The initial Whickham study observed that lipid levels were not associated with TSH elevation after age adjustment[10]. The Colorado study and others noted significantly elevated LDL cholesterol in subjects with subclinical hypothyroidism[16,38]. A report from Rotterdam noted that subclinical hypothyroidism subjects actually had lower total cholesterol[12].

Women with subclinical hypothyroidism did not differ from controls with regard to hypertension, and diabetes in the previous studies[12,51]. The present study also showed it to be true.

A recent analysis concluded that screening for and treating mild thyroid failure in all adults over 35 years of age is as cost-effective as many other screening procedures[59]. There is documented evidence that many (but not all) effects are improved or corrected when L-thyroxine replacement is instituted. L-thyroxine treatment was recommended for the majority of patients with mild thyroid failure, particularly those with symptoms, goiter, positive thyroid antibodies, and those who are pregnant. However, despite these positive indications that treatment carries some benefits, the benefit-to-risk ratio of treatment remains to be determined, given the lack of outcome data and the considerable risk of TSH suppression in patients on L-thyroxine replacement.

CONCLUSION

- Subclinical hypothyroidism is highly prevalent in elderly women above the age of 50 years (29.2%). Most of those with subclinical hypothyroidism have the TSH level below 10 µIU/ml.
- Mild symptoms of hypothyroidism are prevalent in patients with subclinical hypothyroidism (29% of patients in this study). Fatigability being the most common symptom.
- Patients with subclinical hypothyroidism are more prone to develop ischemic heart disease.
- There is no increased risk for developing hypertension and diabetes mellitus in patients with subclinical hypothyroidism.

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PROFORMA

NAME: IP NO:

AGE: ADDRESS:

SEX: OCCUPATION:

HISTORY OF

- Fatigability
- Weight gain
- Constipation
- Cold intolerance

PAST HISTORY:

- Hypertension
- Diabetes mellitus
- Coronary heart disease
- Hypothyroidism
- Drug intake
- Exposure to irradiation
- Thyroid surgery

PERSONAL HISTORY:

1. Menstrual history
2. Obstetric history

CLINICAL EXAMINATION:

Pulse rate Blood pressure Goiter

CVS:

RS:

ABDOMEN:

CNS:

INVESTIGATION:

- FT3, FT4, TSH
- Fasting blood sugar
- ECG

Figure 1.

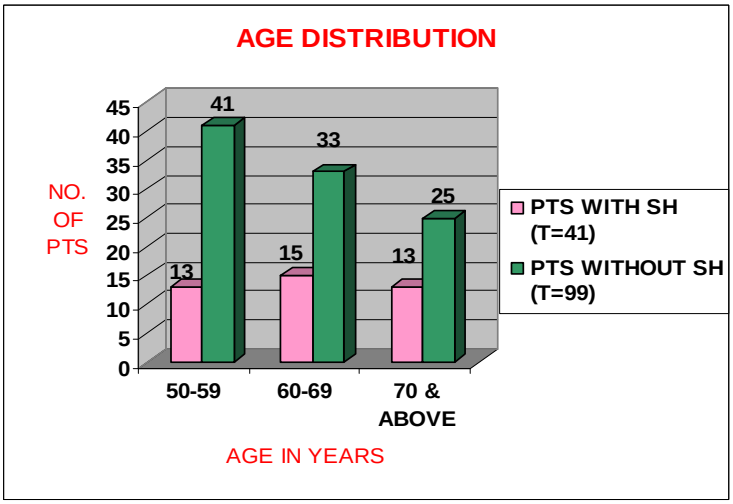


Figure 2.

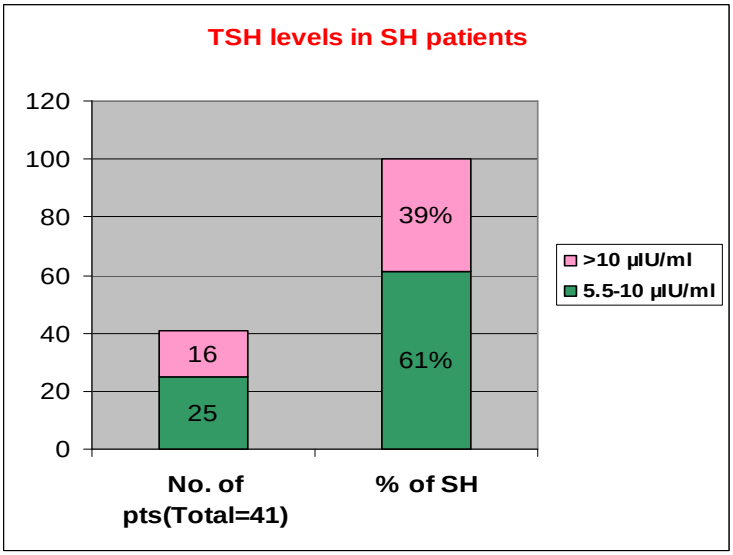


Figure 3

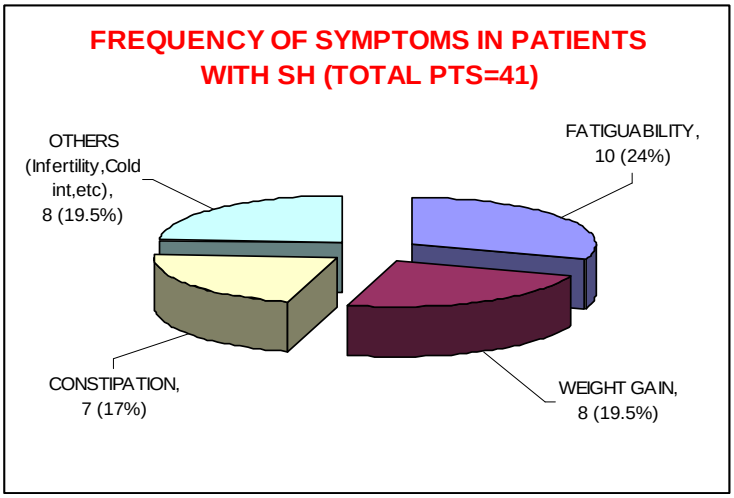


Figure 4.

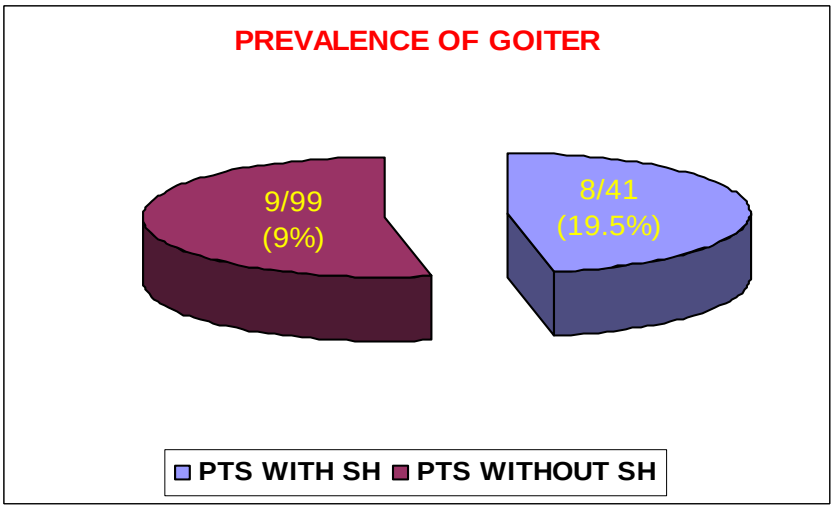
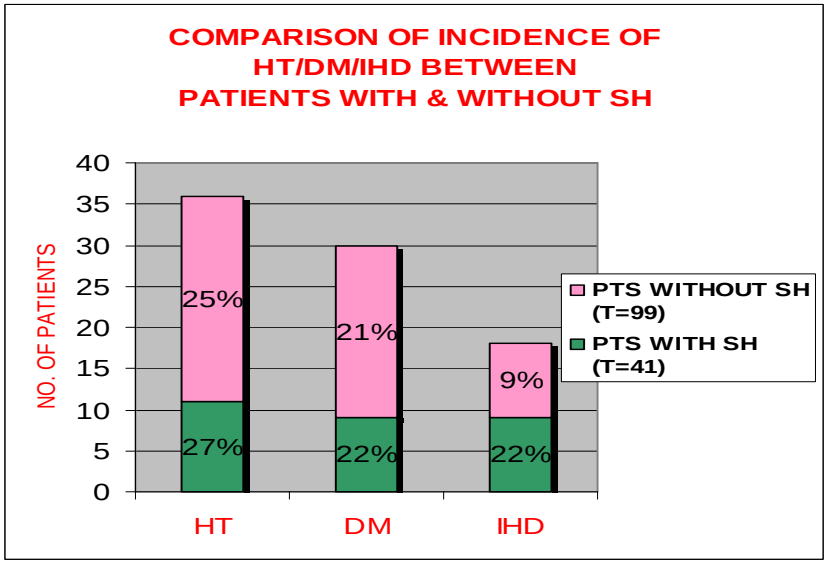


Figure 5.



MASTER CHART

PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

S.NO	AGE	FT3	FT4	TSH	HT	DM	IHD	FATIGABILITY	CONSTIPATION	WEIGHT GAIN	OTHER SYMPTOMS	GOITER
1	55	3.42	0.72	14.84	+	-	+	-	-	-	-	-
2	64	1.96	0.78	9.4	-	-	-	-	-	-	-	-
3	61	2.2	1.12	8.04	-	-	-	-	-	-	-	+
4	65	1.96	0.88	13.5	+	-	-	-	-	-	-	-
5	58	2.46	0.96	7.04	-	+	+	-	-	-	-	-
6	73	3.96	0.8	6.21	+	-	-	-	-	-	-	-
7	53	3.64	0.98	8.92	-	-	-	-	-	-	-	-
8	64	3.2	0.84	10.82	-	-	-	+	-	+	+	-
9	55	2.24	1.24	9.02	-	-	-	-	-	-	-	-
10	75	3.26	0.88	7.72	-	+	+	-	-	-	-	-
11	63	3.12	0.96	15.42	+	-	-	+	+	+	+	+
12	54	2.36	0.92	8.48	-	-	-	-	-	-	-	-
13	77	3.44	1.34	7.62	-	-	+	-	-	-	-	-
14	58	2.44	1.64	8.26	-	-	-	-	-	-	-	+
15	79	3.26	1.24	31.33	+	+	-	-	+	+	+	-
16	57	3.38	0.92	7.62	-	-	-	-	-	-	-	-
17	71	3.86	0.78	6.9	-	-	-	-	-	-	-	-
18	66	4.02	1.24	19.17	-	-	+	-	-	-	-	-
19	52	3.32	1.44	9.24	+	+	-	-	-	-	-	-
20	74	3.24	1.42	20.36	-	-	-	+	+	+	-	+

S.NO	AGE	FT3	FT4	TSH	HT	DM	IHD	FATIGABILITY	CONSTIPATION	WEIGHT GAIN	OTHER SYMPTOMS	GOITER
21	57	2.1	1.4	8.46	-	-	-	-	-	-	-	-
22	62	3.7	1.46	13.93	-	+	+	-	-	-	-	-
23	67	2.68	0.88	17.5	-	-	-	-	-	-	-	-
24	58	3.28	0.92	8.4	-	-	-	-	-	-	-	-
25	76	1.92	0.88	12.62	-	-	-	+	+	-	+	+
26	65	1.96	0.96	9.38	-	-	-	-	-	-	-	-
27	73	1.88	0.92	28.82	+	+	-	+	+	+	-	-
28	59	2.08	0.98	8.42	+	+	-	-	-	-	-	-
29	61	1.82	0.96	31.38	+	-	-	+	+	-	+	-
30	51	2.22	0.86	9.4	-	-	+	-	-	-	-	-
31	66	3.26	1.14	7.62	-	-	-	-	-	-	-	-
32	67	1.98	1.02	5.81	-	+	-	-	-	-	-	-
33	72	1.88	0.92	11.23	-	-	-	+	+	-	+	+
34	70	2.12	0.94	7.86	-	-	-	-	-	-	-	-
35	53	1.92	0.88	9.22	-	-	-	-	-	+	+	-
36	60	1.82	0.82	16.23	-	-	-	+	-	+	-	+
37	68	1.92	0.98	8.32	-	+	+	-	-	-	-	-
38	76	2.26	0.92	7.64	-	-	-	-	-	-	-	-
39	78	2.08	0.96	9.86	-	-	-	-	-	-	-	-
40	69	2.18	0.92	11.72	+	-	-	+	-	-	-	+
41	72	2.14	0.84	10.86	+	-	+	+	-	+	+	-

PATIENTS WITHOUT SUBCLINICAL HYPOTHYROIDISM

S. NO	AGE	FT3	FT4	TSH	HT	DM	IHD	GOITER
1	65	2.48	0.82	4.6	-	-	-	-
2	62	4.1	1.62	3.82	-	-	-	-
3	52	3.24	1.04	4.16	-	+	-	-
4	71	1.84	1.24	5.12	-	-	-	+
5	58	2.6	1.54	3.44	+	-	-	-
6	72	2.24	0.94	4.6	-	-	-	-
7	66	3.72	0.82	2.18	+	-	-	-
8	77	3.4	1.62	4.72	+	+	-	-
9	68	3.42	1.42	4.24	+	-	-	+
10	51	3.12	0.9	2.86	-	-	-	-
11	67	2.88	1.24	5.12	-	-	-	-
12	76	3.4	1.32	4.76	-	-	-	-
13	52	4.04	0.92	3.53	-	-	-	-
14	78	2.62	0.92	2.08	+	-	+	-
15	53	1.94	0.92	4.81	-	-	-	-
16	79	1.88	0.88	3.6	-	-	-	-
17	59	2.42	1.12	3.14	-	-	-	-
18	69	3.12	1.06	4.88	-	+	-	-
19	74	1.96	1.32	3.86	-	-	-	-
20	69	2.4	0.96	2.62	+	-	-	+
21	52	2.42	0.82	3.6	-	-	-	-
22	60	2.26	1.06	2.06	-	+	+	-
23	78	1.94	1.28	5.32	-	-	-	-

S. NO	AGE	FT3	FT4	TSH	HT	DM	IHD	GOITER
24	56	2.82	0.98	3.22	-	-	-	-
25	73	2.64	0.82	2.76	-	+	+	-
26	66	2.92	1.08	5.12	-	-	-	-
27	68	3.68	1.32	4.66	-	-	-	-
28	52	1.88	1.12	3.42	-	-	-	-
29	57	3.34	1.32	2.74	+	-	-	-
30	61	3.94	0.86	0.92	-	-	-	-
31	75	3.88	0.92	4.78	-	-	-	-
32	67	2.68	1.32	5.44	-	-	-	-
33	70	2.94	0.88	1.68	+	-	-	-
34	51	2.62	1.16	4.08	-	+	+	-
35	62	3.42	0.88	0.98	-	-	-	-
36	78	3.88	0.86	3.28	-	-	-	-
37	57	2.68	0.98	4.3	-	-	-	-
38	56	3.54	0.92	5.14	+	-	-	-
39	69	2.82	1.62	4.5	-	-	-	-
40	71	1.96	1.34	2.68	-	-	-	-
41	75	3.32	0.76	4.86	-	-	-	-
42	51	2.84	0.88	3.8	-	+	-	-
43	63	2.76	1.16	4.36	+	-	-	-
44	79	3.4	1.08	1.6	-	-	-	+
45	56	1.96	0.94	3.42	-	-	-	-
46	55	2.88	0.86	2.88	-	-	-	-
47	68	3.92	1.6	4.24	-	+	-	-
48	72	4.02	1.56	2.24	+	+	-	+
49	59	3.24	1.42	3.62	-	-	-	-

S. NO	AGE	FT3	FT4	TSH	HT	DM	IHD	GOITER
50	64	2.46	1.08	4.48	-	-	-	-
51	51	4.08	0.98	4.6	-	-	-	-
52	73	3.88	1.24	2.74	-	+	+	-
53	54	2.92	1.12	4.15	+	+	-	-
54	65	3.76	1.46	4.26	-	-	-	-
55	76	2.96	0.96	5.16	-	-	-	-
56	66	2.14	0.98	4.44	-	-	-	-
57	53	3.82	1.16	2.24	-	+	+	-
58	51	2.76	1.24	3.08	-	+	-	-
59	55	3.34	0.96	4.72	-	-	-	-
60	58	2.86	1.32	3.68	-	-	-	-
61	66	3.62	1.44	2.72	-	-	-	-
62	74	3.82	1.08	2.86	-	-	-	-
63	50	1.96	1.26	3.82	-	-	-	-
64	53	2.42	1.06	2.94	-	-	-	-
65	65	3.32	1.18	3.46	+	-	-	-
66	52	3.82	0.96	4.34	+	-	-	-
67	75	3.66	1.32	2.44	+	+	-	-
68	67	1.88	1.46	3.38	-	-	-	+
69	57	2.6	1.22	5.22	+	-	-	-
70	67	1.86	1.24	4.84	-	+	+	-
71	51	2.42	1.42	4.26	+	-	-	-
72	76	3.26	1.34	1.56	-	-	-	-
73	73	3.34	1.12	5.2	-	-	-	+
74	50	3.26	0.98	4.72	-	-	-	-
75	63	4.04	0.88	2.64	-	-	-	-

S. NO	AGE	FT3	FT4	TSH	HT	DM	IHD	GOITER
76	56	3.62	1.42	3.82	-	-	-	-
77	69	2.14	1.08	4.46	-	+	+	-
78	77	3.26	1.26	2.74	+	-	-	-
79	54	3.82	1.18	3.62	-	+	-	-
80	68	2.68	1.22	5.4	-	-	-	-
81	59	2.84	1.64	3.76	+	-	-	-
82	64	2.26	1.42	5.18	+	-	+	+
83	55	3.42	1.18	1.12	-	-	-	-
84	51	3.84	0.98	2.32	-	-	-	-
85	63	1.96	1.42	3.28	-	-	-	-
86	54	2.24	1.36	4.76	-	-	-	-
87	78	3.62	1.06	1.86	+	+	-	-
88	58	3.44	0.92	2.38	+	-	-	-
89	60	2.84	1.04	3.82	+	-	-	-
90	55	3.26	1.22	4.4	-	-	-	+
91	52	2.98	1.42	1.24	-	-	-	-
92	53	3.28	1.18	4.68	-	-	-	-
93	74	2.24	0.82	3.56	-	-	-	-
94	58	3.42	1.24	5.24	-	-	-	-
95	64	2.98	1.38	3.86	+	+	-	-
96	61	3.12	0.98	4.24	-	-	-	-
97	56	2.96	1.4	1.74	+	+	-	-
98	65	3.4	1.28	3.64	-	+	-	-
99	62	3.62	1.14	3.8	-	-	-	-